Glucosamine, Chondroitin, and Manganese Ascorbate for Degenerative Joint Disease of the Knee or Low Back: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Objective: A 16-week randomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCl (1,500 mg/day), chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) in degenerative joint disease (DJD) of the knee or low back was conducted. Methods: Thirty-four males from the U.S. Navy diving and special warfare community with chronic pain and radiographic DJD of the knee or low back were randomized. A summary disease score incorporated results of pain and functional questionnaires, physical examination scores, and running times. Changes were presented as a percentage of the patient's average score. Results: Knee osteoarthritis symptoms were relieved as demonstrated by the summary disease score (−16.3%; $p = 0.05$), patient assessment of treatment effect ($p = 0.02$), visual analog scale for pain recorded at clinic visits (−26.6%; $p = 0.05$) and in a diary (−28.6%; $p = 0.02$), and physical examination score (−43.3%; $p = 0.01$). Running times did not change. The study neither demonstrated, nor excluded, a benefit for spinal DJD. Side effect frequency was similar to that at baseline. There were no hematologic effects. Conclusions: The combination therapy relieves symptoms of knee osteoarthritis. A larger data set is needed to determine the value of this therapy for spinal DJD. Short-term combination therapy appears safe in this setting.

Introduction

The most common cause of articular morbidity is degenerative joint disease (DJD), which results from the inability of articular structures to withstand applied stress. This process begins because the articular structures are abnormal or because the stress is unusually high.[1] Eventually, both become pathologic, as the stress induces metabolic and structural changes in the articular cartilage and other tissues, and joint deterioration results in abnormal biomechanical loading. In synovial joints, articular cartilage experiences a loss of proteoglycans, disruption of the collagen matrix, and increased hydration.[1,2] DJD includes synovial joint osteoarthritis, such as in the knee and spinal apophyseal (facet) joints, and degenerative disease of cartilaginous joints, such as the intervertebral discs.[1]

Standard medical therapy includes nonsteroidal anti-inflammatory agents (NSAIDs), which provide analgesia and reduce secondary synovial membrane inflammation.[3] However, NSAIDs have well-known side effects. It is possible that some NSAIDs may accelerate disease progression through adverse effects on cartilage metabolism or joint overuse associated with analgesia.[2-5]

An alternative approach is to administer substances extracted from cartilage that are reputed to facilitate cartilage repair, with or without cofactors involved in tissue repair. The goal is to reduce immediate symptoms and long-term disease progression by stimulating proteoglycan production and cartilage healing. For example, there has been interest outside of North America for many years in the use of glucosamine and chondroitin sulfate in DJD. Although the long-term effect on disease progression is not well established, both glucosamine[6-15] and chondroitin sulfate[16-20] have been shown to decrease osteoarthritis symptom severity. In vitro observations suggest that these agents may aid in cartilage production and repair.[3,9,13] Scientific and popular interest in these agents has increased recently in the United States, where they are widely available as nutritional supplements without a prescription, often combined with cofactors such as manganese ascorbate.

Because of the importance of mechanical stress in the pathogenesis of DJD, it is not surprising that overuse, trauma, and certain occupations are associated with DJD. Weight-bearing joints such as the knees and spine are frequently affected. We conducted a placebo-controlled trial of glucosamine, chondroitin sulfate, and manganese ascorbate in DJD of the knee or low back in males in the U.S. Navy diving and special warfare communities. The characteristic aspects of this study were (1) use of the agents in combination, and (2) evaluation in a population with a history of high activity levels and unique occupational exposures.

Subjects and Methods

Subjects

Thirty-four males with chronic knee or low back pain were recruited through fliers posted at U.S. Navy diving and special warfare commands. Inclusion criteria were knee or low back pain on most days for at least 3 months[19] and corresponding degenerative changes on X-ray, such as osteophytes, joint (or disc) space loss, subchondral bone cysts, or subchondral bone sclerosis.[1] Anteroposterior and lateral radiographs were obtained. Patients with prominent patellar symptoms also had axial views. Stage 4 radiographic disease[21,22] was a cause for exclusion. Additional exclusion criteria, and the number ex-

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cluded, are listed in Table I. The study was approved by the Naval Medical Center Portsmouth Committee on Human Investigation, which held the randomization codes until study termination. All volunteers gave written informed consent.

Study Design

The study was a single-center, outpatient, randomized, double-blind, placebo-controlled, crossover trial. After a 3-week baseline run-in period, subjects were randomly allocated to receive one of two capsules: either oral Cosamin (a combination of glucosamine HCl [1,500 mg/day], chondroitin sulfate [1,200 mg/day], and manganese ascorbate [228 mg/day] in three divided doses) or matching placebo capsule for 8 weeks. For an additional 8-week period, patients crossed over to the regimen not followed previously. The capsules were obtained from Nutramax Laboratories (Baltimore, Maryland). Patients continued their normal routines, including physical exercise as tolerated. During the protocol, patients were not permitted NSAIDs but were permitted acetaminophen for pain.[23] Acetaminophen is efficacious for DJD.[24] Permitting only acetaminophen avoided uncertainty regarding whether NSAIDs might alter cartilage metabolism and whether gastrointestinal side effects were attributable to NSAIDs or the test medication. This practice also simplified statistics.

Efficacy

Outcomes were assessed by averaging data from two clinic visits during each study phase (after weeks 2 and 3 of the 3-week baseline period, and after weeks 7 and 8 of both 8-week treatment periods). For each joint, the following were assessed:

—The Lequesne index of severity for knee osteoarthritis[25] or responses to the Roland questionnaire for back disability were determined.[26]
—The patient's assessment of the handicap was scored from 0 (none) and 1 (mild) to 5 (almost unbearable).[25]
—The physician's overall assessment of severity was scored from 0 (none) to 3 (severe).
—The visual analog scale for pain was between 0 and 10 cm,[27] with 1 point assigned for every 2 cm.
—Tenderness with movement of the low back and with firm pressure on the knees was scored from 0 (none) to 3 (severe).[28]
—The time to run 100 yards and to run up and down a tower with 80 stairs, touching every stair, was scored as 1 point for every 10 seconds.
—The physical examination parameters suggested by Pavelka (tenderness with palpation in passive movements, decreased range of motion, warmth, crepitus, effusion, swelling, muscle atrophy)[29] were scored from 0 (none) to 3 (severe).
—Knee active range of motion was assessed by measuring degrees of flexion minus degrees of extension. Lumbar flexion was measured in centimeters using the modified Schober technique because this test has low intrapatient variation.[30] Range of motion was scored as 1 point for every 15° decrease in knee range of motion, and for every 2-cm decrease in lumbar flexion, compared with baseline.
—The patient's assessment of treatment result was scored from −3 (much better) to +3 (much worse), in comparison with the previous phase.[25] For the second treatment phase,

TABLE I

CHARACTERISTICS OF RANDOMIZED, WITHDRAWN, AND EXCLUDED PATIENTS

	Total	Knee	Low Back
Age (years)	43.5 ± 1.7	45.2 ± 2.1	43.6 ± 2.3
Height (cm)	179 ± 1	179 ± 2	180 ± 1
Weight (kg)	87 ± 2	88 ± 3	89 ± 3
Total randomized	34	21	23
Radiographic stage			
<1	–	1	0
1	–	9	10
2	–	9	12
3	–	2	1
Withdrawals (total)	7	3	7
To take NSAID	3	1	3
No time to comply	1	0	1
Military orders to leave area	3	2	3
Patient assessment of treatment result (medication vs. placebo)			
Improved (<0)	14[a]	10[a]	9
Unchanged (0)	16	9	10
Worse (>0)	4	2	4
Excluded from study			
Deployment/duty	7	5	4
No degenerative X-ray change	9	6	5
Stage 4 radiographic disease	0	0	0
Inflammatory arthritis (psoriatic)	1	1	0
Referred for surgery (meniscal tear, positive straight leg raise on examination)	2	1	1
Articular injection/aspiration in previous month	0	0	0

Age, height, and weight data are means ± SEM. Other data are numbers of patients.
[a] $p < 0.05$ by sign test.

this score was stated in comparison with the baseline phase by adding the values for the first and second phases.

The joint summary score was the sum of these scores obtained during the clinic visits. Scaling factors for the running time, visual analog scale, and range of motion were specified in advance.

Subjects also recorded the visual analog scale for pain (0–7 cm) and the acetaminophen dose in a daily diary. Compliance with at least 80% of study medication ingestion, and complete NSAID avoidance, was assessed through the diaries and patient interviews.

Evaluation of Safety

Patients were asked to complete a survey of symptoms consistent with toxicity and to return cards for fecal occult blood testing at the end of each protocol phase. Blood pressure and pulse were measured. Twenty-one patients had determinations of the complete blood count and coagulation studies performed by the Naval Medical Center Portsmouth clinical laboratory at the end of each treatment phase.

Statistical Analysis

Clinic visit scores and diary information for weeks 6 through 8 were evaluated. Outcome measures were normalized by expressing them as a percentage of that patient's mean score for all three phases. After normalization, patients having the same relative change in a parameter had the same score, despite variation in the absolute change. Analyses were conducted for qualifying knee joints in knee patients, spinal disease in low back patients, and all qualifying joints in all randomized patients. The unit of analysis was the patient, not the joint. In other words, for patients with bilateral knee disease or both knee and back disease, the joint scores were averaged to obtain the patient's average score. Treatment efficacy and treatment-period interactions were assessed with the standard two-sample t test.[31] Patient assessment of treatment result was also assessed by the sign test. Other effects (e.g., placebo) were assessed with the matched-pair t test. For all tests, Statistica 5.1 was used (StatSoft, Inc., Tulsa, Oklahoma). The intention-to-treat analysis included all randomized patients. If data were unavailable, the last available information was carried forward.[23,31]

Results

Thirty-four patients were randomized. The demographic characteristics are shown in Table I. Four patients had a history of saturation diving, and six had a history of decompression sickness. No patient had dysbaric osteonecrosis on study radiographs.

Twenty of the 21 qualifying knee patients satisfied standard clinical plus radiographic classification criteria for osteoarthritis.[32] The final patient had radiographic patellar osteopenia, which is occasionally seen in chondromalacia patella,[1] and had previous arthroscopic evidence of chondromalacia patella and medial femoral condyle osteoarthritis. This patient had less than stage 1 radiographic disease (Table I). The most severely affected compartments radiographically were medial tibiofemoral (8 of 21), lateral tibiofemoral (2 of 21), and patellofemoral (11 of 21). Five patients qualified for knee osteoarthritis bilaterally. Of the 21 qualifying knee patients, 18 had knee injuries requiring immobilization and/or knee surgery (86%), 16 had knee surgery (76%), and 10 had partial or total meniscectomies (48%). Parachute landings caused the knee injuries in 6 patients (29%).

Twenty-three qualifying patients with spinal DJD and low back pain were randomized. The predominant radiographic feature was degenerative disc disease in 17 of 23 patients and apophyseal (facet) joint osteoarthritis in 6 of 23 patients. Eleven patients experienced trauma to the low back. In 8 patients, the trauma was associated with a fall related to work (while parachuting, performing helicopter operations, or on the obstacle course). Of the back patients not experiencing trauma, 6 had severe initial injuries or exacerbation of injuries while lifting or doing exercises. Nine patients had radicular symptoms at some time.

There were seven protocol dropouts (Tables I and II). Three knee patients withdrew: two received military orders to leave the area, and one required NSAIDs during the second (placebo) phase.

Efficacy

The improvement in the overall summary score on medication, compared with placebo, approached the standard level of statistical significance ($p = 0.052$; Table III). Statistically significant improvement was seen in the patient assessment of treatment result ($p = 0.02$) and the visual analog scale for pain, whether recorded on examination days ($p = 0.02$) or in the diary ($p = 0.02$). When on medication, 14 patients noted improvement, 4 noted worsening, and the remainder were unchanged, compared with placebo ($p = 0.03$; Table I). On the other hand, trends in physical examination scores, acetaminophen use, disability scores of Lequesne and Roland, patient assessment of handicap, and physician assessment of severity were not significant (Table III). There was essentially no change in running times or range of motion. None of the tests for treatment-period interaction for any outcome or subgroup was significant ($p > 0.05$).

Separating the knee data from the back data, it became clear that the improvements were attributable mainly to improvements in knee symptoms. For the knee, the mean patient assessment of treatment result was −0.89, with a 95% confidence interval (95% CI) of −1.64 to −0.14 ($p = 0.02$), where −1.00 corresponds with the phrase "a little better" (Table III). When on medication, 10 patients noted improvement, 2 noted worsening, and the remainder were unchanged, compared with placebo ($p = 0.04$; Table I). The overall summary score for the knee data showed a mean change compared with placebo of −16.3% (95% CI, −32.5% to −0.05%; $p = 0.049$). The visual analog scale for pain showed a mean change of −26.6% during the clinic visits (95% CI, −53.0% to −0.2%; $p = 0.048$) and −28.6% in the diary data (95% CI, −52.7% to −4.5%; $p = 0.02$). The physical examination score showed a mean change of −43.3% (95% CI, −74.5% to −12.1%; $p = 0.01$). Changes in the physical examination subscores of tenderness, effusion, swelling, and warmth did not reach significance when considered individually. Trends in acetaminophen use, Lequesne scores, and patient and physician assessment of severity did not reach significance. The running times and knee range of motion did not change.

TABLE II

SYMPTOMS, PHYSIOLOGIC VARIABLES, AND WITHDRAWALS BY TREATMENT PHASE

	Treatment Phase			
	Baseline	Placebo	Medication	M vs P[a]
Answered symptom questions	32	29	28	–
Fatigue	6	2	4	–
Cough	2	2	1	–
Skin irritation, flushing, itching	5	3	3	–
Weakness	1	0	1	–
Nausea, upset stomach, heartburn	2	1	2	–
Stool changes or flatulence	1	3	1	–
Rectal bleeding	3	1	2	–
Dark tarry stools, tremor, or vomiting	0	0	0	–
Total number of symptoms	20	12	14	2
Withdrawals				
On protocol at start of phase	34	31	31	–
Began NSAIDs during phase	0	2	1	–
Military orders to leave area	0	1	2	–
No time to comply	0	1	0	–
Total withdrawals during phase	0	4	3	−1
Fecal occult blood evaluated	29	27	24	–
Occult blood positive	1	0	0	0
Vital signs at both treatment phases	–	27	27	27
Mean blood pressure (mmHg)	–	97.0 ± 2.0	97.2 ± 2.1	±2.6
Pulse (bpm)	–	68.4 ± 1.7	70.0 ± 1.6	±1.7
Hematology evaluated	–	21	21	21
Hematocrit (%)	–	43.9 ± 0.7	44.0 ± 0.7	±0.2
Hemoglobin (g/dL)	–	15.1 ± 0.2	15.1 ± 0.2	±0.1
Red blood cell (10^{12}/L)	–	4.84 ± 0.06	4.85 ± 0.07	±0.03
White blood cell (10^9/L)	–	6.6 ± 0.5	6.4 ± 0.3	±0.4
Platelet (10^9/L)	–	232 ± 8	235 ± 8	±7
Prothrombin time (s)	–	10.6 ± 0.1	10.7 ± 0.1	±0.1
Partial thromboplastin time (s)	–	29.1 ± 0.3	29.1 ± 0.5	±0.5

Symptom and withdrawal data are numbers of patients. Vital signs and hematology data are means ± SEM. No changes significant ($p > 0.05$).
[a]Medication phase versus placebo phase.

None of the trends for benefit in low back pain reached significance (Table III). On the other hand, the 95% CI values for the overall summary score (−26.3% to +7.3%) and the patient assessment of treatment effect (−1.34 to +0.10) were wide and did not exclude the possibility of meaningful benefit.

Safety

No patients reported symptoms requiring termination of the study, and symptom frequency on medication was similar to that at baseline (Table II). The vital signs, occult blood testing, and hematologic parameters did not change significantly from placebo to medication (Table II).

Discussion

This study demonstrated the effectiveness of an over-the-counter combination of glucosamine HCl, chondroitin sulfate, and manganese ascorbate in relieving symptoms of knee osteoarthritis. On the other hand, this small study neither demonstrated, nor excluded, the possibility of benefit in spinal DJD. The drug was well tolerated, and there was no evidence of adverse hematologic effects.

The relief of knee discomfort was the most important finding in this study. Osteoarthritis of the knee is not unexpected in this occupational setting given the history of high levels of activity and trauma. The risk of knee osteoarthritis is increased by occupational overuse, for example, by kneeling, squatting, and climbing stairs,[33] and by trauma[1] severe enough to require immobilization[34] or surgery,[1] specifically meniscectomy.[1,34] The relief of knee symptoms was indicated by the summary scores, the patient overall assessment of treatment effect, the visual analog scales for pain in the clinic and in the diary, and the physical examination scores. About half of the knee patients noted improvement compared with placebo (Table I). The lack of evidence of benefit in the Lequesne score or the assessment of handicap was not surprising, because the initial values were low enough that they were probably not sensitive in this population. The absence of improvement in running scores was a disappointment. Other osteoarthritis protocols noted improvements in stair climbing[35] and level walking times.[14,35]

The spine is susceptible not only to osteoarthritis in the synovial apophyseal (facet) joints but also to degenerative disease of the intervertebral discs, which are cartilaginous joints. Spinal osteophytosis is more common in heavy physical laborers.[36] With the possible exception of disc-space loss, most studies do not demonstrate degenerative radiographic findings to be more common in patients with low back pain than in patients without

TABLE III

PLACEBO AND TREATMENT EFFECTS FOR DEGENERATIVE JOINT DISEASE

Measurement	Baseline	Placebo vs. Baseline	Medication vs. Baseline	Medication vs. Placebo
Summary score				
Total	22.7 ± 1.1	−13.2 ± 6.1%*	−25.3 ± 6.9%	−12.1 ± 6.0%†
Knee	24.5 ± 1.5	−8.2 ± 7.1%	−24.5 ± 8.4%	−16.3 ± 7.8%*
Back	22.6 ± 1.4	−10.7 ± 7.7%	−21.2 ± 8.5%	−9.5 ± 8.1%
Patient assessment of treatment result				
Total	–	−0.11 ± 0.28	−0.74 ± 0.28	−0.63 ± 0.26*
Knee	–	−0.07 ± 0.34	−0.95 ± 0.39	−0.89 ± 0.36*
Back	–	−0.17 ± 0.37	−0.44 ± 0.33	−0.62 ± 0.35
Visual analog scale for pain (clinic visit, 0–10 cm)				
Total	4.6 ± 0.4	−23.5 ± 15.0%	−50.8 ± 13.7%	−27.3 ± 11.5%*
Knee	4.1 ± 0.4	−15.7 ± 14.0%	−42.5 ± 14.3%	−26.6 ± 12.6%*
Back	5.1 ± 0.4	−19.2 ± 18.8%	−48.4 ± 17.8%	−28.0 ± 15.4%
Visual analog scale for pain (diary, 0–7 cm)				
Total	2.6 ± 0.2	−20.4 ± 11.0%	−42.3 ± 9.9%	−21.9 ± 8.6%**
Knee	2.7 ± 0.2	−9.8 ± 10.1%	−38.4 ± 13.2%	−28.6 ± 11.5%*
Back	2.7 ± 0.3	−19.5 ± 14.4%	−41.4 ± 10.9%	−21.0 ± 11.4%
Physical examination score				
Total	1.93 ± 0.24	3.4 ± 6.2%	−11.4 ± 14.3%	−14.8 ± 13.9%
Knee	2.93 ± 0.39	2.4 ± 13.3%	−41.1 ± 15.4%	−43.3 ± 14.9%**
Back	1.30 ± 0.21	8.9 ± 6.4%	13.7 ± 17.8%	6.6 ± 19.3%
Acetaminophen (g/week)				
Total	2.51 ± 0.85	3.7 ± 20.8%	−26.0 ± 17.9%	−29.7 ± 19.5%
Knee	3.05 ± 1.38	12.2 ± 26.7%	−15.8 ± 24.2%	−30.6 ± 23.2%
Back	3.36 ± 1.21	2.2 ± 20.7%	−22.1 ± 22.8%	−21.8 ± 25.2%
Disability questionnaire				
Total	6.6 ± 0.6	−29.1 ± 11.6%**	−42.9 ± 13.5%	−13.7 ± 8.1%
Knee (Lequesne)	6.9 ± 0.6	−9.8 ± 11.9%	−23.2 ± 14.1%	−13.7 ± 9.8%
Back (Roland)	6.9 ± 0.8	−32.1 ± 14.3%	−47.7 ± 17.0%	−13.7 ± 11.3%
Patient assessment of handicap				
Total	2.2 ± 0.1	−16.1 ± 5.4%**	−22.0 ± 5.1%	−5.9 ± 5.6%
Knee	2.3 ± 0.1	−19.0 ± 6.8%**	−25.0 ± 7.1%	−6.5 ± 7.3%
Back	2.3 ± 0.2	−7.5 ± 5.5%	−17.1 ± 6.3%	−7.6 ± 7.3%
Physician overall assessment of severity				
Total	1.5 ± 0.1	−0.3 ± 5.0%	−12.0 ± 6.6%	−11.7 ± 7.3%
Knee	1.6 ± 0.1	2.8 ± 5.9%	−17.5 ± 11.1%	−19.9 ± 10.7%
Back	1.5 ± 0.1	−3.0 ± 6.3%	−5.5 ± 5.7%	−9.2 ± 7.9%
100-yard run (seconds)				
Total	19.8 ± 1.8	−10.3 ± 5.5%	−9.5 ± 5.5%	0.8 ± 2.9%
Knee	22.1 ± 2.7	−15.2 ± 8.7%	−16.5 ± 8.1%	−0.9 ± 3.7%
Back	18.2 ± 1.6	−1.8 ± 4.0%	−1.4 ± 3.2%	−0.0 ± 4.4%
Stair-climbing time (seconds)				
Total	52.3 ± 1.4	−4.8 ± 1.6%**	−4.8 ± 1.7%	−0.0 ± 2.2%
Knee	53.5 ± 2.1	−4.9 ± 2.4%†	−4.8 ± 2.7%	0.4 ± 3.5%
Back	52.4 ± 1.8	−4.4 ± 2.2%	−4.1 ± 2.5%	−0.3 ± 3.2%
Range of motion				
Knee (degrees)	127 ± 3	−0.4 ± 1.2%	−1.0 ± 1.2%	−0.6 ± 1.3%
Back flexion (cm)	21.0 ± 0.2	−0.3 ± 0.7%	−0.6 ± 1.2%	−0.1 ± 0.9%

Data are means ± SEM. Units for baseline scores are defined in the text. Placebo and medication phase scores are change from baseline as a percentage of the patient's average for all three phases, except patient assessment of treatment result, which is a relative point score (−3 to +3). Statistical significance of placebo relative to baseline, or treatment relative to placebo: †approaching significance ($p < 0.06$); *$p < 0.05$; **$p < 0.02$; otherwise $p > 0.06$.

pain.[36] Nonetheless, patients with a combination of chronic pain and degenerative radiographic findings form a reasonable group for initial study of these agents.[8] One preliminary study demonstrated the efficacy of oral glucosamine for spinal osteoarthritis symptoms.[8] A significant proportion of the patients in another positive study of oral glucosamine had lumbar or cervical disease.[7] The nonsignificant trend in the current small study is interesting, and the data may help in designing larger follow-up trials.

Most physicians in the United States are probably not familiar with the use of these agents in DJD. Glucosamine is probably the best supported for oral use. Glucosamine sulfate forms half

of the disaccharide subunit of keratan sulfate, which is decreased in osteoarthritis,[2] and of hyaluronic acid, which forms the backbone of proteoglycan aggregates in articular cartilage and is found in high concentration in the synovial fluid. Recent studies[9,13] reviewed evidence that: (1) glucosamine increases production of glycosaminoglycans and proteoglycans by fibroblasts and chondrocytes, and (2) in animal models, glucosamine has mild prostaglandin-independent anti-inflammatory effects but no analgesic effects. Oral[14] C-labeled glucosamine sulfate is well absorbed: 11% of radioactivity appears in feces, 10% appears in urine, and the area under the curve of radioactivity in plasma is 26% of that after intravenous administration.[37] Randomized, placebo-controlled trials demonstrated symptomatic relief by glucosamine given orally,[6-9] intra-articularly,[10] or intramuscularly[11] for DJD of the knee[6,9-11] and other joints.[7,8] Compared with NSAIDs[12,13] or NSAIDs followed by placebo,[14,15] glucosamine eventually produced similar[13] or superior[12,14,15] results for DJD of the knee[12,13] and other joints,[15] although the relief with glucosamine occurred more slowly.[12,13]

Chondroitin sulfate, one of the predominant glycosaminoglycans in articular cartilage, is a polymer of the repeating disaccharide unit of galactosamine sulfate and glucuronic acid. Some studies have used a glycosaminoglycan polysulfate (GAGPS) preparation, commercially available as Arteparon,[3,35] which consists primarily of oversulfated chondroitin.[3] GAGPS has been shown to inhibit several enzymes with the potential to degrade collagen and proteoglycans.[3] GAGPS stimulates chondrocyte synthesis of proteoglycan, collagen, and hyaluronic acid.[3] Parenteral GAGPS reduces abnormalities of cartilage structure and metabolism in animal models of osteoarthritis.[3] Randomized, placebo-controlled studies demonstrate that intramuscular,[16-18] intra-articular,[38] and oral[19] chondroitin sulfate[16-19] and GAGPS[38] reduce symptoms of DJD of the knee[16-19,38] and the hip.[19] Oral chondroitin sulfate was more effective than diclofenac sodium followed by placebo for knee osteoarthritis, although the chondroitin sulfate regimen worked more slowly.[20] GAGPS decreased symptoms and radiologic progression of knee osteoarthritis with intramuscular administration.[35] The control group did not receive placebo injections, group assignment was based on date of presentation, and it is difficult to know if the findings apply to oral administration. Although oral chondroitin sulfate reduces symptoms,[19,20] the mechanism is controversial. The area under the curve of colorimetrically determined chondroitin sulfate in plasma after an oral dose was 13.2% of that after an intravenous dose.[39] In dogs given oral ^{3}H-labeled chondroitin sulfate, about 12% of radioactivity was found in the urine and 15% in the feces.[40] Others found no evidence of absorption of sulfated forms and postulated that any mechanism for efficacy resides in the gastrointestinal tract.[41]

Ascorbate is a cofactor in the hydroxylation of procollagen,[2] and deficiencies result in poor wound healing. Ascorbic acid has been shown to help with osteoarthritis in some animal models, but it was one component of a regimen that failed to improve osteoarthritis symptoms in humans.[42]

Manganese is incorporated in many commercial preparations, presumably because deficiencies result in formation of abnormal bone and cartilage.[43] Evidence of efficacy in degenerative joint disease when used alone is lacking.

Safety and Dosage

The 1,500-mg daily oral dose of glucosamine was standard.[6-9,12,13,15,44] An open investigation of glucosamine in 1,208 patients showed it to be tolerated by 86% of patients.[44] Most side effects were gastrointestinal (e.g., heartburn, diarrhea, nausea, vomiting).[44]

Chondroitin sulfate can be given at 1,200 mg/day,[20,45] as used in the current study, or 2,000 mg/day.[19] In one open experience, the only side effect of oral chondroitin sulfate was nausea in 3% of patients.[45]

Hematologic effects have been a concern. Chondroitin sulfate and GAGPS have a heparinoid structure.[3] Parenteral glycosaminoglycans can prolong the prothrombin time and the partial thromboplastin time and decrease platelet aggregability.[46] A number of trials noted no significant effects on the complete blood count[7,12,15,45] when oral glucosamine[7,12,15] or oral chondroitin sulfate[45] were given separately. In dogs, the combination oral preparation produced minor transient decreases in hematocrit and white blood cell count, decreases in platelet count and aggregability, but no change in bleeding or clotting times.[46] Despite statistical significance of some changes, values stayed within the normal clinical range.[46] The present study detected no statistical or clinical changes in the complete blood count or clotting time with a lower weight-adjusted dose of the combination oral preparation in humans.

Manganese toxicity after oral ingestion is unlikely because of poor absorption,[43] and no signs of toxicity were apparent in this study (e.g., hypertension, cough, tremor, weakness). The daily manganese dose in the tested preparation (approximately 30 mg) exceeds the 2.5- to 5-mg range deemed safe and adequate.[47] The justification for a supraphysiologic dose in a commercial preparation is unclear.

Limitations

Post-treatment carryover effects may cause difficulty with crossover trials[13] and lead to underestimation of the benefit. The present study attempted to minimize these effects by allowing a 5-week washout period for the diary data and a 7-week washout period for the clinic visit data. The absence of treatment-period interactions argued against the importance of carryover effects. As the current and previous[16] work demonstrate, despite the potential for carryover effects, benefits may be detected in small studies because of the increased precision associated with the crossover design.

Patients who find a test medication ineffective may be more likely to withdraw from a randomized trial. However, in this crossover study in a military setting, those who withdrew before ever beginning the medication phase, or because of military orders to leave the area, did not withdraw because of lack of treatment effect. Five of seven total withdrawals, and two of three knee patient withdrawals, fell into one or both of these categories. The intention-to-treat analysis assumed that these patients found the medication ineffective, and was therefore conservative.

Given that standard radiographs are insensitive for detecting degenerative changes compared with pathologic specimens[32] or other imaging techniques,[36] future studies may focus on the benefit of these agents for patients before evidence of joint damage is present on standard radiographs.

Other areas for further study include (1) the long-term effect on disease progression, (2) the benefit in spinal DJD, (3) cost-effectiveness, and (4) interactions of the component agents with each other and with NSAIDs.

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